Handling of Certain important Solutes by the Renal Tubules

Na^+ Handling by the Renal Tubules

Na^+ is filtered in large amounts through the glomeruli, but Na^+ is reabsorbed out of all portions of the tubule except the thin descending segment of the loop of Henle.

96% to well over 99% of the filtered Na^+ is reabsorbed.

90% of the energy consumed by kidney is used for active transport of Na^+. The reabsorption of Na+ is coupled with:

- Reabsorption of most of the solutes in the filtrate by secondary active mechanism or by diffusion.
- Reabsorption of H_2O by osmosis.
- Secretion of K^+.
- HCO_3^- reabsorption and H^+ secretion.

- ***Na^+ Reabsorption in the Different Segments of the Renal Tubule:***

Figure (4-1) shows Na^+ handling in the nephron, and the percentages of the filtered load reabsorbed by different segments:

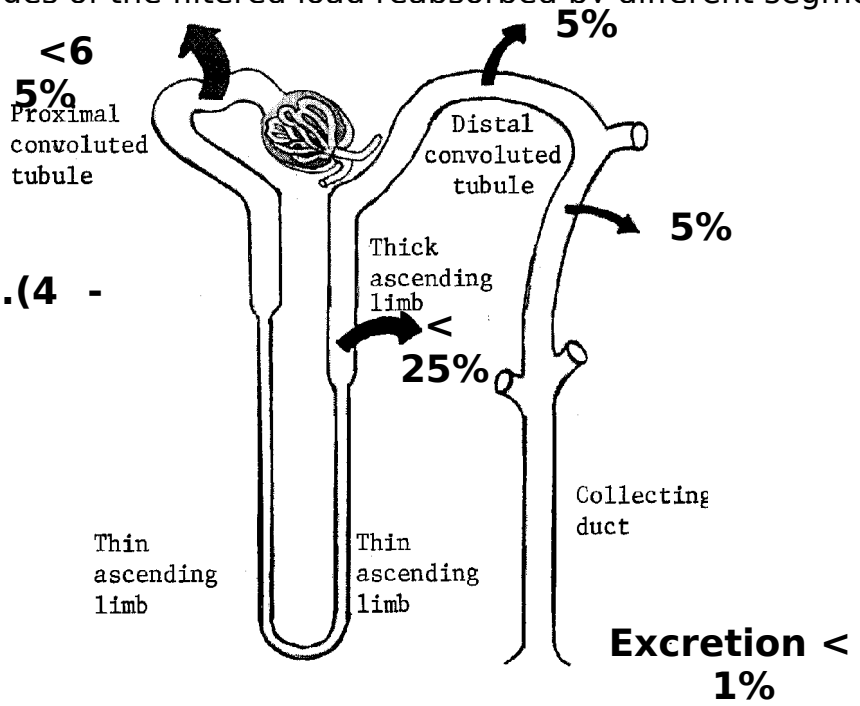

Fig.(4 - 1)

1. Proximal Tubule:

65% of the filtered load of Na^+ is reabsorbed by the proximal tubule.

This reabsorptive process is active and depends on the action of the basolateral membrane Na^+ K^+ -pump, to keep intracellular Na^+ concentration low.

Although Na^+ reabsorption by PCT is an active process (Page: 32), it has no tubular maximum, but obeys the gradient-time transport because the rate of its transport at the basolateral borders of the cells is a greater than the rate of its diffusion at the brush border. Early and late proximal tubules are different as regards the anions and other solutes that accompany Na^+.

a) First half of The Proximal Tubule:

Na^+ is reabsorbed by co-transport along with glucose, amino acids, sulphate, Pi, organic acids (lactate and citrate) and HCO_3 (Fig. 4-2).

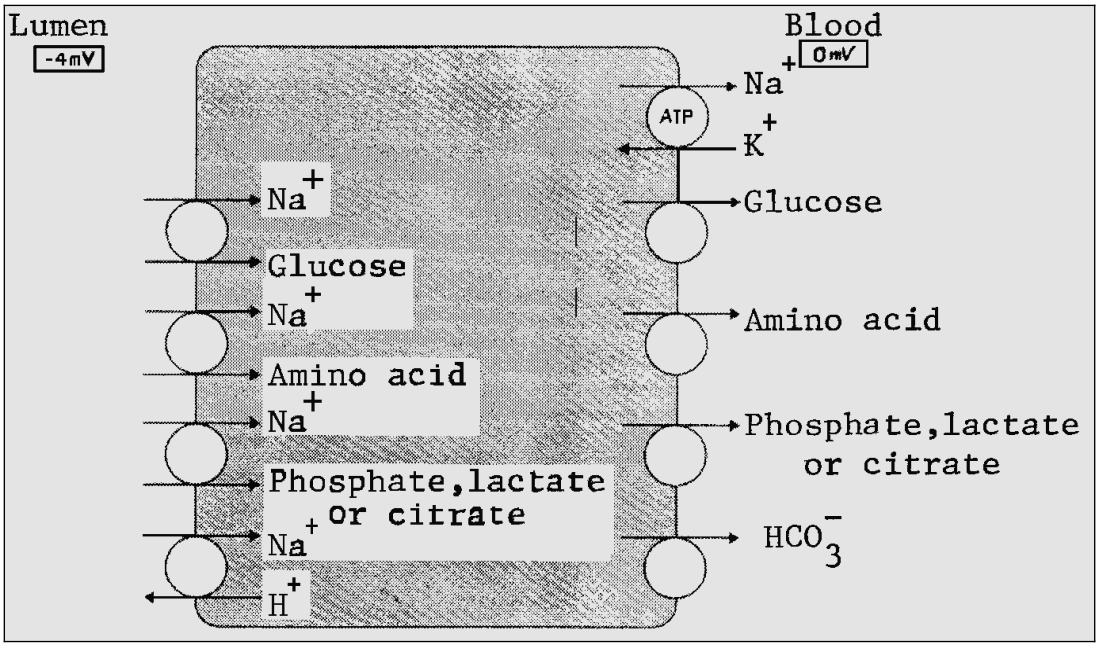

Fig. (4-2)

- These cotransport processes account for the reabsorption of all the filtered glucose and amino acids.
- Na^+ is also reabsorbed by counter transport via N^+-H^+ exchange which is linked directly to the reabsorption of filtered HCO_3^-. (Fig. 4-3).

Reabsorption of Na^+ across the luminal membrane is accompanied by H^+ secretion via Na^+ - H^+ counter-transport.

H^+ secretion is accompanied by HCO_3^-reabsorption. (Fig. 4-3).

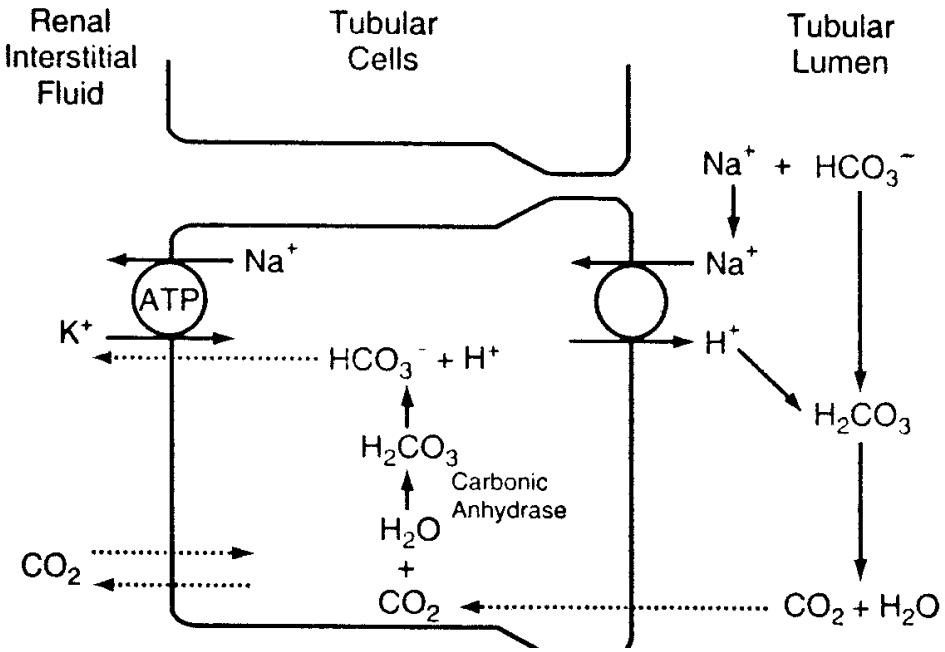

Fig. (4-3)

- ***Within the proximal tubule cell:***

$$CO_2 + H_2O \xrightleftharpoons{CA} H_2CO_3 \dashrightarrow H^+ + HCO_3^-$$

H^+ is secreted into the tubular lumen where it combines with filtered HCO_3^- to form ultimately $C0_2$ + H_2O under influence of CA in the luminal membrane.

For each H^+ ion that is secreted, one HCO3$^-$ ion generated

within the proximal tubule cell which is transported across basolateral membrane into the peritubular capillaries.

b) Late half of The Proximal Tubule:

Na^+ is reabsorbed with chloride ion (Cl^-). The late proximal tubule reabsorbs primarily NaCl.

2- *Loop of Henle and early distal tubule:*

- ***Thin descending limb:***

Reabsorb water, but has no capacity to reabsorb Na^+ as the Na^+ transport proteins or channels are absent from luminal membrane.

- ***Thin Ascending limb:***

Reabsorption of NaCl in the thin asending limb in passive by concentration gradient.

The thin ascending limb of the loop of Henle is impermeable to water. As a result, tubular fluid [Na+] and tubular osmolarity decreases. This segment is called the diluting segment,

- ***Thick ascending limb and early distal tubule:***

25% of the filtered load of Na^+, K^+, and Cl^- are reabsorbed by co-transport mechanism, that co-transports one Na^+ one K^+ and two Cl^- from the lumen into the cells. (Fig. 4-4)

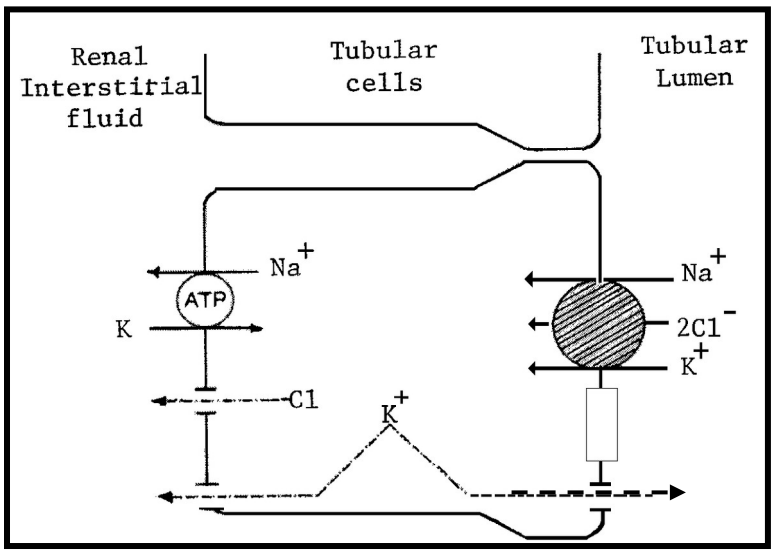

Fig. (4-5)

(Fig.4-4)

Most of the K^+ that enters the cell refluxes back into the lumen via K^+ channels and it serves two purposes:

a) It ensures a sufficient concentration of K^+ for optimal function of the co-transporter.

b) The resulting net positive potential in the lumen facilitates paracellular reabsorption of several cations including Na^+, K^+, Ca^{++}, and Mg^{++}.

Reabsorption of NaCl in the thin ascending limb is passive by concentration gradient.

- ***Bartter's Syndrome:***

Cause: Defect in the Na^+ - K^+ - 2 Cl^- cotransporter in the luminal membrane of the thick ascending limb Loss of Na^+, K^+, Cl^-, and ***calcium.***

Manifestations:

- Renal salt wasting.
- Volume depletion.
- Hypokalemia.
- Metabolic alkalosis.
- Hypercalciuria.

3- ***Early distal tubule:***

- Is called the cortical diluting segment.
- Reabsorption NaCl by a Na^+-Cl^- cotransporter.
- Is impermeable to water, as is the thick ascending limb. Thus, reabsorption of NaCl occurs without water which further dilutes the tubular fluid.

4- *Late Distal Tubule and Collecting Duct:*

Less than 10 % of the filtered Na^+ is reabsorbed by the late distal tubule and collecting duct.

The principal cells are responsible for reabsorption of Na^+ in exchange with K^+ secretion.

The rate of reabsorption of Na^+ is controlled by aldosterone.

Mechanism: Na^+ diffuses into the principal cells through Na^+ channels in the apical membrane, while K^+ diffuse into the tubular fluid across luminal membrane down its concentration gradient.

Na^+ is extruded from the cell vial Na^+ - K^+ ATPase in the basolateral membrane. The anion that accompanies Na^+ is mainly Cl^-. The concomitant reabsorption of Cl^- is paracellular, and is driven by the luminal negative potential that results from Na^+ transport. (Fig. 4-5).

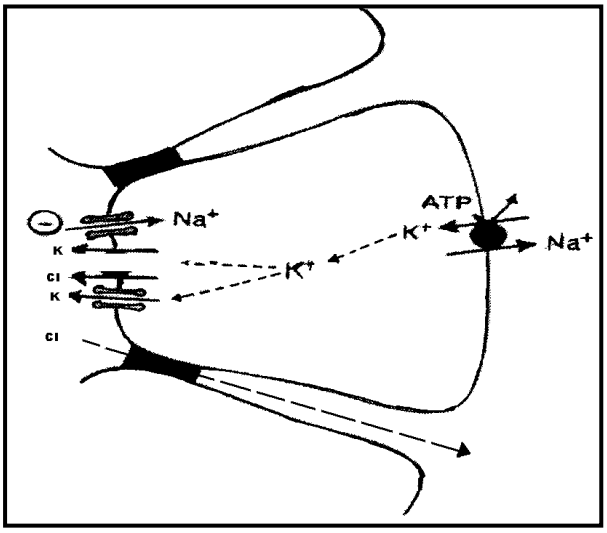

Fig. (4-5)

- **Regulation of Na^+ Excretion:**

Na^+ is the main cation in ECF. Sodium salts accounts for over 90% of the osmotically active solutes in the plasma and interstitial fluid.

The amount of Na^+ excreted is adjusted to equal the amount

ingested over a wide range of dietary intake.

Thus, the urinary Na^+ output ranges from 1 mEq/day on a low-salt diet to 400 mEq/day or more when the dietary Na^+ intake is high.

- **Variations in Na^+ excretion are affected by:**

1. Amount filtered.
2. Amount reabsorbed.

Therefore, factors that influence GFR and tubular reabsorption will affect renal excretion of Na^+

1. Glomerular Filtration Rate:

"Glomerulotubular Balance"

Definition .An increase in GFR causes an increase in the reabsorption of solutes and consequently of water.

Site: the main site is the proximal convoluted tubule. Loop of Henle also shares.

The mechanism occurs independent of hormones and can occur in isolated kidney.

This process is prominent for Na^+ and it shows that the renal tubules reabsorb a constant percentage of the filtered Na^+ (2/3 or 65%) rather than a constant amount

- ***Importance:***

a- It helps to prevent overloading of the distal tubular segment when GFR increase

b- It prevents inappropriate losses of Na^+ and water in the urine that can occur as a result of sudden increase in GFR.

Thus, increased GFR increases the amount of Na^+ filtered and this increases the amount reabsorbed leading to a slight increase in Na^+ excretion.

It represents the ability of the proximal tubule to reabsorb a constant percentage of the filtered load of Na^+ and water.

2. Rate of Tubular Flow:

Slow rate of flow will increase tubular reabsorption of Na^+ as in cases of decreased GFR.

3. Effect of ABP on tubular reabsorption "Pressure Natruresis" and "Pressure Diuresis":

Pressure Natruresis: An increase in ABP cause marked increase in urinary excretion of Na^+ and water.

* ***Mechanism:***

1. Decreased angiotensin II secretion with rise of ABP.
2. Backleak of Na^+ into the tubular lumen due to:

a) Rise of hydrostatic pressure in peritubular capillaries with rise of ABP.

b) Rise in the interstitial fluid hydrosataic pressure as a consequence of the rise in hydrostatic pressure in the peritubular capillaries. An increase in the renal interstitial fluid hydrostatic pressure enhance backleak of sodium into the tubular lumen, thereby reducing the net reabsorption of sodium and water and further increasing the rate of urine output when arterial pressure rises.

This is primarily a compensatory mechanism for regulation of ABP independent of nervous or hormonal influence.

4. Hormonal Control:

(A) Hormones that increases Na^+ reabsorption:

(I)

- Aldo ange with K^+ or H^+

- It ac t (Fig. 4-6).

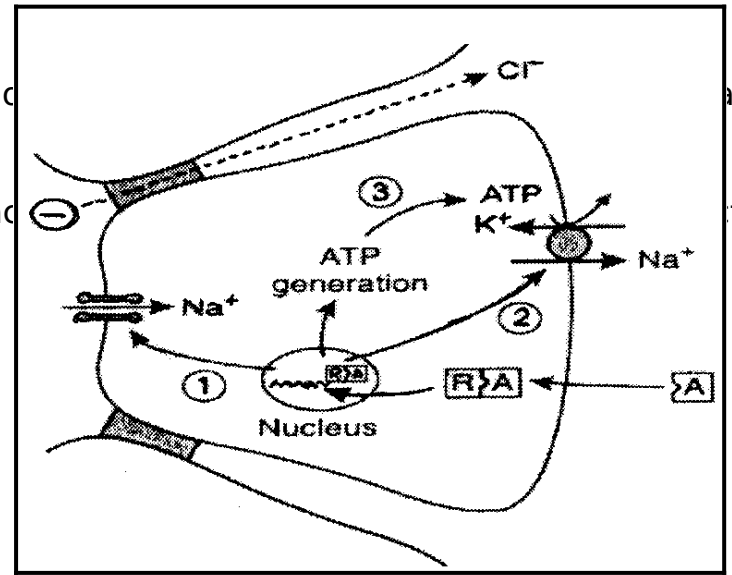

Fig. (4-6): Intracellular mechanism of action of Aldosterone in the collecting ducts.

They act on P cells that contain sodium channels in their apical membranes.

- *Aldosterone acts through:*

i) Increase number of Na^+ channels in the luminal membrane.

ii) Increase number of Na^+-K^+ ATPase molecules in the basal membrane.

(II) Glucocorticoids:

Cortisol has weak mineralocorticoid activity.

(III) Angiotensin II:

It is the most powerful sodium-retaining hormone, it increases Na^+ reabsorption:

i) *Angiotensin II* stimulates aldosterone secretion.

ii) *Direct action on PCT cells:*

- Stimulates Na^+ - K^+ ATPase pump.

- Stimulates Na^+ - H^+ counter transport.

iii) *Constricts efferent arterioles:* this help to increase Na^+

and water reabsorption by peritubular capillaries:

- Reduce hydrostatic pressure in peritubular capillaries.
- Increase osmotic pressure of peritubular capillaries through increasing filtration fraction.

(IV) Sex Hormones:

Estrogen increases Na^+ reabsorption by renal tubule.

(B) Hormones that decreases Na^+ reabsorption:

(I) ANP:

ANP facilitates the excretion of NaCl and water under conditions of marked expansion of ECF.

Mechanism:

- Increases GFR ➔ increases filtered Na^+ ➔ ++Na^+ excretion. It increases GFR by:
  - Relaxation of the mesangial cells➔ increases surface area for filtration.
  - VD of the afferent arteriole.
- Inhibit renin secretion: This in turn reduces the levels ofangiotensin II and the levels of aldosterone.
- Inhibit Na+ reabsorption by collecting ducts by direct effect:
  - Inhibit Na^+ - channels in the apical membrane.
  - Inhibit Na^+ - K^+ ATPase in the basolateral membrane.

(II) PGE2: Increase Na^+ excretion through:

i) Inhibit Na^+ *channels in the apical membrane.*

ii) Inhibit Na^+ - K^+ *ATPase in the basolateral membrane.*

(III) Endothelin: Increases PGE_2. (Fig. 4-7).

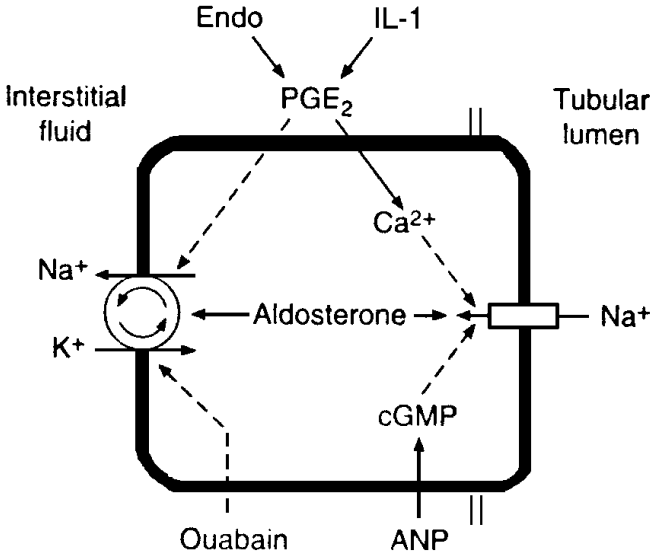

Fig. (4-7)

5. **Sympathetic stimulation: Increases Na^+ reabsorption and decreases Na^+ excretion:**

   a) Reduce GFR by constricting renal vessels.

   b) Increases renin secretion and 'angiotensin II formation ➔increases Na^+ reabsorption

   c) Increases Na^+ reabsorption by the proximal tubule and thick ascending limb of Loop of Henle.

6. **Diuretics:** Increase Na^+ excretion (see later, Page 58).

Glucose reabsorption by the renal tubules

Site: Normally all of the filtered glucose is reabsorbed in the early portion of the proximal convoluted tubule. Only few milligrams appear in urine per 24 hours.

Mechanism: Secondary active transport, i.e. secondary to the primary active transport of Na^+:

** At the luminal border:*

Glucose and Na^+ bind to a common carrier SGLT-2 (Sodium-

dependent glucose transporter) in the luminal membrane. As Na^+ moves down its chemical and electrical gradient, glucose is carried into the cells.

This transport is dependent on Na^+. Transport at the luminal border can be blocked by:

Oubain : blocks Na^+ - K^+ ATPase.

Phlorhizin : competes with glucose for SGLT-2 carrier.

** At the basolateral border:*

Glucose is carried into the interstitium by facilitated diffusion down chemical gradient. The carrier is GIUT-2 (glucose transporter).

- **Tubular Transport Maximum (T_m):**

* T_{mG} : is defined as the maximum amount of glucose (in mg) that can be reabsorbed by the renal tubules per minute.

* It is an indication of the reabsorptive capacity of the kidney and is determined by the number of glucose carriers in the proximal tubule.

* Value: T_{mG} : 300 mg / min in female.

375 mg / min in male.

*** Renal threshold for glucose:**

The plasma level at which glucose first appears in the urine than the normal minute amounts.

*** Value:**

Arterial blood: 200 mg / dl

Venous blood: 180 mg / dl

*** Glucose Titration Curve and T_m:**

Glucose titration curve depicts the relationship between plasma glucose concentration and glucose reabsorption. (Fig. 4-8)

The filtered load of glucose and the excretion rate of glucose are plotted on the same graph.

The glucose titration curve is obtained experimentally by infusion of glucose and measuring its rate of reabsorption as the plasma concentration is increased.

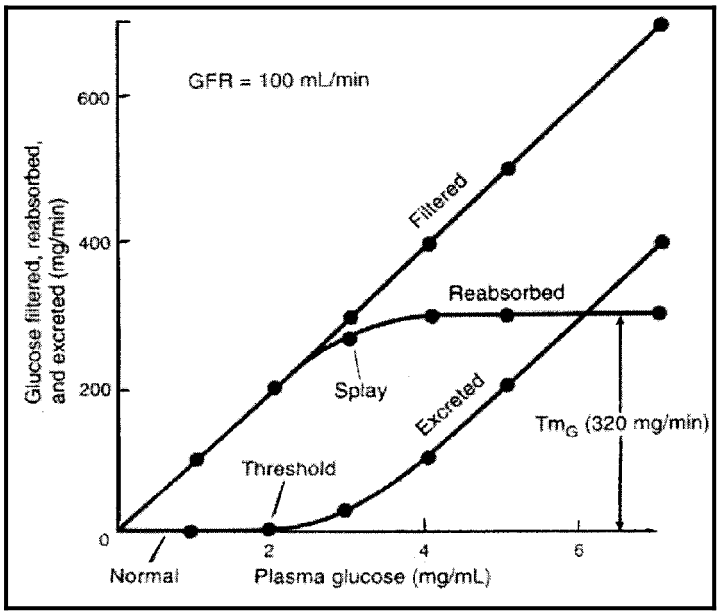

Fig. (4-8): Tubular transport maximum for glucose.

The titration curve is best understood by examining each relationship separately and then considering all three relationships together.

*** Filtered load of glucose:**

Glucose is freely filtered across glomerular capillaries, and the filtered load is the product of GFR and plasma glucose concentration [P] glucose-Filtered load = GFR x [P] glucose

Thus, as the plasma glucose concentration is increased, the filtered load increases linearly.

*** Reabsorption of glucose:**

- At the plasma glucose concentration less than 200 mg/dl, all of the filtered glucose can be reabsorbed because Na^+ glucose transporters are plentiful. In this range the curve for reabsorption is identical to that for filtration, i.e. reabsorption equals filtration.
- At the plasma glucose concentration above 200 mg/dl the reabsorption curve bends because some of the filtered glucose is not reabsorbed as there are a limited number of Na^+-glucose carriers.
- At the plasma glucose concentrations above 300 mg/dl, the carriers are completely saturated and reabsorption reaches its maximal value T_m.

  Therefore, increases in plasma concentration above 300 mg/dL do not result in increased rates of reabsorption. T_m is the point at which the carriers are saturated.

*** Excretion of glucose:**

To understand the curve for excretion, compare those for filtration and reabsorption as follows:

- Below plasma glucose concentration of 200 mg/dl, all of the filtered glucose is reabsorbed and none is excreted.
- Above plasma glucose concentrations of 200 mg/dl, the carriers are nearing the saturation point. Most of the filtered glucose is reabsorbed, but some is not; the glucose that is not reabsorbed is excreted.
- Above 300 mg/dl, Tm is reached and the carriers are fully saturated. Therefore, as the plasma concentration increases the addition of filtered glucose cannot be reabsorbed and is excreted in the urine. The curve for excretion now increases linearly paralleling that for filtration.
- The plasma glucose concentration at which glucose is first

excreted in the urine is called threshold, which occurs at a lower plasma concentration than does T_m.

The T_m for glucose is approached gradually, rather than sharply producing the splay. Splay is that portion of the titration curve where reabsorption is approaching saturation, but it is not fully saturated. Splay is the region of the reabsorption curve between threshold and T_m and occurs between plasma glucose concentration of approximately 200 and 300 mg/dL. The explanation of the splay is as follow:

Splay is due to heterogeneity of the nephrons: Tm for the whole kidney reflects the average T_m of all nephrons, yet all nephrons do not have exactly the same T_m. Some nephrons will reach Tm at lower plasma concentration than others, and glucose will be excreted in the urine before the average Tm is reached.

Glycosuria

It is excretion of glucose in urine in considerable amounts.

* ***Causes:***

1) Diabetes Mellitus:

Glycosuria occurs when the blood glucose level is elevated and exceeds renal threshold.

2) Renal glycosuria:

Glycosuria occurs at normal plasma glucose level. The renal threshold for glucose is lowered below 180 mg % due to congenital defect in the glucose transport mechanism in the renal tubule. T_{mG} is markedly decreased in renal glycosuria. Excretion of the osmotically active glucose molecule entails the loss of large amounts of water (osmotic diuresis) with loss of Na^+ and K^+.